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tation that results from the pentameric structure of IgM is its limited ability to diffuse rapidly from sites of local production to distant sites (8). For this reason, and because of its short *in vivo* half-life relative to IgG (9,10), existing IgM antibodies are probably less well adapted than IgG antibodies to protect against second infections by a pathogen.

Antibodies of the IgG, IgA, and IgE isotypes are made later than IgM antibodies during a primary immune response, but account for most of the antibody that is produced during a memory response. Although isotype switching and affinity maturation are independent processes, they usually occur simultaneously (11), so that the affinity of bivalent antibodies of isotypes other than IgM is great enough to allow for high-avidity binding of antigen. IgG antibodies are the predominant isotype in plasma and extravascular lymph (12), while IgA antibodies predominate in respiratory, digestive, and urogenital secretions (13).

IgG Subclasses

The different IgG subclasses share a long half-life, which facilitates the maintenance of high serum IgG levels. In mouse, rat, and human, the different IgG subclasses differ in effector function. Complement is fixed most effectively by IgG2a and IgG2b in the mouse (14,15), IgG2b in the rat (16), and IgG1 and IgG3 in the human (17,18). Mouse IgG3 and possibly IgG1; rat IgG1, IgG2a, and IgG2c; and human IgG2 antibodies also have some ability to fix complement (16). Rodent and human IgG subclasses also differ in their abilities to bind to Fcγ receptors. FcγRI, which is expressed on rodent monocytes and macrophages, binds mouse IgG2a and rat IgG2b with high affinity (19–21). Mouse FcγRII (on macrophages, monocytes, B lymphocytes, mast cells, and some T lymphocytes) and FcγRIII (on macrophages, neutrophils, mast cells, and NK cells) bind mouse IgG2b > IgG2a > IgG1, all with low affinity (20,22). None of these receptors bind mouse IgG3 effectively. Human FcγRI (on monocytes, macrophages, and neutrophils) binds IgG1 and IgG3 most avidly and IgG2 to a lesser degree (20,22–24). Human FcγRII (on macrophages, monocytes, neutrophils, and B cells) and FcγRIII (on monocytes, macrophages, NK cells, neutrophils, and some T cells) selectively bind, with low affinity, IgG1 and IgG3 (20,22). In addition, some IgG isotypes (IgG1 in the mouse, IgG2a in the rat) bind to mast cell receptors and can mediate mast cell degranulation (25,26). IgG isotypes also bind to placental Fc receptors, which facilitate transport of maternal IgG (but not other isotypes) into the fetal circulation (27).

Different antigenic stimuli induce the production of different IgG subclasses. Soluble protein antigens stimulate predominantly IgG1 responses in the mouse (28,29), while carbohydrate antigens induce substantial IgG3 responses in the mouse (28,30), IgG2c responses in the rat (31), and IgG2 responses in the human (32–34). Viruses induce mostly IgG2a responses in the mouse (35), and IgG1 and IgG3 responses in the human (36). Gram-negative bacteria induce IgG2a and, to some extent, IgG3 responses in the mouse (37–39). Nematode parasites induce predominantly IgG1 responses in most mouse strains (40) and are associated with IgG4 responses in the human (41,42). Repeated immunization also tends to induce humans to produce IgG4 antibodies (43).

To some extent, the functional properties of particular IgG subclasses appear to make them particularly well suited to the binding or destroying of particular types of antigen or parasite. The ability of mouse IgG2a to effectively fix complement, to bind to the macrophage high-affinity receptor for IgG, and to interact with NK cell Fcγ receptors would seem to make it particularly well suited to the control of viral and gram-negative bacterial infections. The ability of mouse IgG3 to self-aggregate *after* binding to an antigen that expresses repeated carbohydrate epitopes (44) allows it, unlike IgM, to diffuse easily into sites of bacterial invasion and, like IgM, to form high-avidity interactions with bacterial cell wall carbohydrate antigens, even though carbohydrate antigens tend to induce low-affinity antibody responses. However, human IgG2 antibodies, despite their association with carbohydrate antigens, have not been found to have this autoaggregating feature (44). The ability of mouse IgG1 antibodies to mediate mast cell degranulation may confer increased resistance to nematode parasites, which typically induce mucosal mast cell responses.

Functional properties that might be expected to enhance the ability of an Ig isotype to destroy a pathogen may also, however, contribute to its potential to damage the host. The autoaggregating properties of mouse IgG3 antibodies appear to make them more likely than other isotypes to be cryoglobulins that cause vascular damage and glomerulonephritis (45). The ability of human IgG1 and IgG3 antibodies to bind to Fcγ receptors makes them, rather than IgG2 and IgG4 antibodies, mediators of erythrocyte destruction in patients with hemolytic disease of the newborn (46). The ability of mouse IgG1 to mediate mast cell degranulation may contribute to its ability to induce anaphylaxis (47).

The correlation, however, between functional properties of individual Ig isotypes and their expression in response to different antigens or pathogens should not be taken as evidence that individual IgG subclasses are essential for protection against different pathogens. Rabbits, for example, produce only a single IgG isotype (48), yet appear to be immunologically competent. It is possible, however, that the multiple IgA isotypes produced by rabbits substitute for the diversity of IgG isotypes that

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